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08/270,152

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/270,152	07/01/94	BOUSSIOTIS	V RPI022

EXAMINER: GAMBEL, P

ART UNIT	PAPER NUMBER
1816	11

DATE MAILED: 03/18/96

18N1/0318

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 12/6/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 48-96 are pending in the application.
   Of the above, claims 62-96 are withdrawn from consideration.
2. ☑ Claims 1-44 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 48-61 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

15. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1816.

16. Claims 1-44 have been canceled.
Claims 48-96 have been added.

Applicant's election with traverse of Group I with the species election of anti-gamma chain antibody in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the newly regrouped claims for modulating unresponsiveness by a T cell. This is not found persuasive because applicant has simply rephrased the claims in terms of modulating unresponsiveness. However, the method claims, drawn to modulating T cell unresponsiveness are still distinct and independent inventions, wherein the endpoint and the diseases differ whether the modulation is either to stimulate (tumors, pathogens) or to inhibit T cells (transplantation and autoimmunity); as pointed out in the last Office Action, mailed 10/4/95 (Paper No. 8). Also, methods of intracellular and extracellular intervention as well as screening methods are held as distinct and independent inventions.

In the interest of compact prosecution, the examiner will examine those current claims that read on applicant's elected invention drawn to methods for stimulating proliferation of a T cell which expresses a cytokine receptor gamma chain; not methods of stimulating T cells intracellularly via an agent that does not bind to an extracellular portion of γ_c (claims 62-70), not methods for inducing unresponsiveness (claims 71-76, 82-96), not methods for inducing unresponsiveness intracellularly (77-81) and not methods for identifying an agent that inhibit delivery a signal thorough a cytokine receptor gamma chain (45-47). The appropriate species election among the different agents and different therapeutic endpoints would also apply, as indicated in the previous Office Action, mailed 10/4/95 (Paper No. 8).
The requirement is still deemed proper and is therefore made FINAL.

Claims 45-96 are pending.

Claims 48-61 are considered drawn to original elected invention of stimulating proliferation of a T cell which expresses a cytokine receptor gamma chain

Non-elected claims 45-47 and 62-96 are held to be withdrawn from further consideration under 37 CFR 1.142(b).

As indicated below, methods of modulating unresponsiveness by a T cell is rejected under 112, first and second paragraph, because it does not clearly recite the intended endpoint of the elected invention, methods of stimulating T cells.

17. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

18. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

19. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. The specification is objected to and claims 48-61 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vitro experimental conditions accurately reflects the relative efficacy of the claimed therapeutic strategy to stimulate T cells, (inhibit unresponsiveness).

Pharmaceutical therapies are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known

or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Applicant provides data wherein the addition of IL-2, IL-4 or IL-7 to the primary culture of T cell clones prevention the induction of anergy. The experimental data also indicates that cross-linking of γ_c during the primary culture prevented the induction of anergy and resulting in both proliferation and IL-2 secretion during rechallenge. Although this provides some evidence that after T cell receptor signaling, an event mediated through the γ_c prevents the induction of anergic state, this analysis only helps to begin to decipher the molecular mechanisms associated with T cell anergy (Boussiotis et al. Science, 1994; last paragraph).

However, there is insufficient information or nexus of how to use this information in the generation of therapeutic methods to prevent unresponsiveness of T cells. Applicant's experimental evidence relies upon well defined culture conditions using T cell lines. However, there is no evidence that such an experimental model mimics the clinical situation; therefore, the predictive value of such an in vitro model remains unknown.

In addressing the complexity of controlling targeting gamma systems; Russell et al. (Science, 1993; see entire document, particularly page 1882, column 3, paragraph 1). Certain activation events, such as B7 expression on B cells and T cell proliferation, can be induced by IL-2 or IL-4. Conversely, IL-4 inhibits IL-2 binding to some cell lines and IL-2 mediated growth. Depending on the amount used, IL-4 can either augment or inhibit IL-2 mediated generation of natural killer cells. These findings may be explained by the differential recruitment of γ into one system and its concomitant sequestration from the other.

In using cytokines such as IL-4 or IL-7 to treat tumors, the parenteral administration of a cytokine to a tumor-bearing animal is compromised by the short half life of the factor and the need to obtain the cytokine in quantities sufficient to achieve effective dose levels. There is insufficient evidence that the available in vitro or vivo data would predict a systemic anti-tumor effect for cytokines or γ_c-specific antibodies administered to such animals.

Applicant's methods are drawn to treating pathological conditions associated with tumor, pathogens, bacteria and viruses. However, these conditions are diagnosed and treated after tumor or infectious agents are already in place. Applicant appears to be claiming the prevention of anergy or tolerance (e.g. unresponsiveness); however there are multiple mechanisms associated with the lack of an effective immune response to such pathological conditions. It is not clear that applicant's reference to inhibiting unresponsiveness is an appropriate mechanism associated with the targeted diseases or that one could intervene at an appropriate stage. For example, tumors comprise self antigens that would not be recognize as foreign; such tolerogenic mechanisms to self antigens occur long before exposure to any pathogen or tumor in an adult.

Therefore, applicant has not provided sufficient evidence that indicates that there is window of opportunity to inhibit unresponsiveness and that such unresponsiveness (lack of costimulation) is critical to the diseases, encompassed by the claimed methods. Generally, such diseases are diagnosed only after significant pathology has occurred. Furthermore, there appears to be a lack of predictability associated with the agents such as the cytokines to treating the conditions, encompassed by the claimed methods. With respect to applicant's elected invention, the disclosed experimental evidence requires cross-linking of γ_c-specific antibodies to stimulate T cells. There is insufficient evidence of an appropriate agent other than γ_c-specific antibodies, IL-4 and IL-7; as applicant's evidence indicates other agents do not inhibit unresponsiveness. Applicant should limit claims to these agents. However, there is a lack of evidence that one could provide sufficient cross-linking at an appropriate time point in vivo to inhibit unresponsiveness or to stimulate any T cell. Similarly, the effectiveness of the cytokines themselves rely upon appropriate local concentrations.

The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering agents an agent which modulates a signal associated with ligation of the cytokine receptor γ_c. The specification does not teach how to extrapolate data obtained from in vitro assays associated with the molecular mechanisms of unresponsiveness in T cell lines to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective pathogen- and tumor- based therapies relying upon cytokine signalling, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting unresponsiveness of T cells in vivo.

21. Claims 48-61 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48-61 are indefinite in the entire recitation of base claim 48 as well as the phrases "modulating unresponsiveness by a T cell", "unresponsiveness by the T cell is inhibited", and "under conditions which normally result in unresponsiveness in a T cell. The claims are vague and indefinite because the language is confusing and inappropriate for the claimed therapeutic endpoints. The claims should reflect the elected invention, which is simply methods of stimulating T cells. Applicant's current claims recite stimulation by applying a double negative, that is, inhibiting unresponsiveness. Also, unresponsiveness in the immunology can refer to immunological tolerance which is not necessarily the case associated with the claimed therapeutic endpoints of tumor and pathogens. Although tumors may not rejected because they are viewed as self which in turn would be immunological tolerance; this occurs at the fetal/neonatal stages of life and is not the same for adult animals. Applicant's invention is drawn to treating diseases in adult animals. Although applicant refers to unresponsiveness as a lack of costimulation, it is not clear that costimulation alone is responsible for the disease processes targeted. Furthermore, applicant's invention is drawn to stimulating T cells to alleviate any lack of costimulation. Therefore, applicant should claim what the invention is, that is, methods for stimulating T cells. Modulation is not appropriate because modulation can occur both in positive and negative directions and applicant elected methods of stimulating T cells. Although applicant claims are directed to conditions which normally results in unresponsiveness in a T cell, however such conditions are ill-defined and only appear to reflect treating tumors or pathogens. There is insufficient information or predictability associated

with such conditions. Applicant is reminded of other 112, first paragraph, issues presented above. Applicant should amend the claims from their current confusing language to a clear positive recitation of the elected and claimed methods.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

22. Claim 48-61 and 56-57 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 56-57 are indefinite in that their recitation does not further limit the claimed methods.

B) As indicated above, applicant should amend the claims from their current confusing and inappropriate language of using double negatives (e.g. to inhibit unresponsivess) to a clear positive recitation of the elected and claimed methods. The methods should set forth clear, distinct and positive process steps with a step that clearly relates to the preamble of the claim.

The amendments must be supported by the specification so as not to add any new matter.

23. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed

publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

25. Claims 48-53, 55-58 and 60-61 are rejected under 35 U.S.C. § 102(e) as being anticipated by Plunkett et al. (U.S. Patent No. 5,382,427). Plunkett et al. teaches the use of IL-4 to treat tumors (see entire document).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced treatment of tumors with the cytokine IL-4.

26. Claims 48-53 and 55-61 are rejected under 35 U.S.C. § 102(b) as being anticipated by Lee et al. (U.S. Patent No. 5,017,691). Lee et al. teaches the use of IL-4 to enhance the natural defense against various infections and malignancy (see entire document, particularly column 2, lines 34-66; column 20, lines 51-68).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced enhancement of immune responses to infections and tumors with the cytokine IL-4.

27. Claim 48-53 and 55-61 are rejected under 35 U.S.C. § 102(a)(e) as being anticipated by Lynch et al. (U.S. Patent No. 5,229,115). Lynch et al. teach the use of IL-7 in the treatment of an individual with cancer of a viral infection by adoptive immunotherapy with T cells in the presence of IL-7 (see entire document, particularly Summary of the Invention).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods of treating cancer and viral infections with IL-7.

28. Claim 48-53, 59 and 61 are rejected under 35 U.S.C. § 102(e) as being anticipated by Grabstein et al. (U.S. Patent No. 5,464,769). Grabstein et al. teach methods of treating microbial infections in a microbially infected mammal by administering IL-7 (see entire document, particularly Summary of the Invention).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced treatment of microbial infections with IL-7.

29. Claim 54 is free of the prior art, however this claim is rejected under 112, first and second paragraphs, set forth above.

30. No claim is allowed.

31. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4065 or (703) 305-7939.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
March 17, 1996